

ALLOGENEIC ISLET THERAPY FOR DIABETES MELLITUS: ISSUES IN EARLY (PHASE 1) CLINICAL INVESTIGATION

Background:

Clinical studies of allogeneic islet therapy in patients with diabetes have been underway for the last 15 years. The various islet products are in the early (phase 1) stages of clinical investigations. As with other phase 1 studies, the goals of these early clinical investigations of allogeneic islets are to determine safety and potential activity of the islet therapy. Islet-based products span a broad range, including differing physical construction (various forms of device-enclosed as well as unenclosed islets) and cell source (human fetal, human adult, and xenogeneic). However, most allogeneic islet studies have much in common. The following is a brief summary of the more common aspects of phase 1 studies of allogeneic islets, with emphasis on the eligibility criteria, safety and activity assessments.

Eligibility:

The patients in these phase 1 trials have advanced type 1 diabetes. The inclusion criteria generally incorporate:

- negligible endogenous C-peptide level
- significant duration of diabetes (e.g., at least 5 years),
- history of poor diabetes control as evidenced by frequency of hypoglycemic episodes and/or significantly elevated HgA_{1c},
- current immunosuppression because of prior organ (usually kidney) transplantation.

Immunosuppression used for renal transplantation may not be optimal for islet therapy. Additionally, variations in immunosuppressive regimens may make patient to patient comparisons, especially between patients immunosuppressed for other organ transplants, difficult in islet therapy. Consequently, some sponsors are beginning to enroll patients without prior organ transplantation. These patients would begin immunosuppression with receipt of their islet cell therapy. This newly

administered immunosuppression would be an additional risk factor to consider in evaluating islet only therapy.

Optimal donor matching criteria have not been established for islet therapy. Some sponsors have used certain donor matching criteria such as ABO and HLA.

Monitoring:

Safety monitoring consists of both general safety and diabetes-specific outcomes (to gain some initial assurance that the islets do not worsen the disease or cause unexpected toxicities). General safety screening tests include routine blood counts, blood chemistries, serum levels of the immunosuppressive drugs, and clinical/laboratory tests assessing the impact of the immunosuppressive therapy. Diabetes-specific monitoring include glucose diaries (glucose and functional status including hypoglycemic episodes), periodic fasting glucose assessments, integrative glucose evaluations such as HgA_{1c} and/or other glycated proteins. Some protocols specify tests for anti-islet and anti-insulin antibody production. The protocols specify the criteria that will lead to individual dose adjustment or discontinuation of the immunosuppression and criteria that will lead to islet removal (if such is feasible, as may be for some encapsulated islet products). The clinical protocols generally include stopping rules which require the cessation of enrollment for the development of severe or clinically significant toxicity.

Informed consent:

The informed consent documents include a discussion about potential islet therapy procedure risks and the potential infectious disease risks. The consent process also informs prospective study participants of the potential negative impact of the investigational islet therapy upon subsequent other organ transplantation procedures associated with allo-immunization.

Dosing:

The dosage or dosages are based on prior clinical experience (if any), the preclinical data, and product availability (i.e. islet harvest limitations). Although it is critical that the cell dose be measured in a consistent manner, such that procedures are reproducible and the data interpretable, disagreement exists regarding the appropriate dose units to be utilized. In general, the dose units have been stated in either the numbers of islet equivalents (defined morphologically) or the amount of some specified islet functional (secretory) unit. In order to adequately evaluate the islet product and to facilitate safe conduct of the study, dose escalation studies are generally

recommended. However, dose escalation studies may not be possible in situations where limited numbers of islets are available. In addition, the number of islets generated and their actual function may in part reflect the overall quality of the donor pancreas, further complicating the use and interpretation of dosage units in islet therapy. In general, phase I trials involve a single administration of allogeneic islets. In some protocols, intense glucose control is attempted in the peri-transplant period to minimize glucose toxicity to the transplanted islets.

Activity evaluations:

Evaluations of islet activity are similar to the diabetes-specific safety measures. The following are some of the common activity measurements:

- C-peptide measurements (basal and/or stimulated),
- hemoglobin A_{1c} levels,
- glucose tolerance testing,
- insulin usage,
- measures of serum glucose variability,
- occurrence of hypoglycemic episodes (symptomatic and/or determined by a specific glucose level)
- patient diaries

The outcomes following islet administration are usually assessed by comparison to a baseline period. To help minimize the effect of non-product related changes in these measures, patients generally are on a stable insulin regimen prior to transplantation. During the baseline evaluation, potential covariates such as diet, exercise, and even the frequency of clinic evaluations should be similar to those that will be in place when assessed after receipt of the islets. Because of the relatively short duration and the few number of patients enrolled in phase 1 trials, it is usually not possible to convincingly assess treatment-related clinical changes in renal disease, peripheral neuropathy, or macrovascular disease.

Efficacy outcomes:

Although the clinical studies of allogeneic islet cells are still in the early phases, it is important to also consider possible measures of efficacy for phase 2 and phase 3 trials. Insulin independence is generally the ultimate goal of islet therapy; however, other outcomes, such as improved glucose control may be potential efficacy endpoints. This may be particularly important in brittle diabetics with a history of life-threatening hypoglycemic episodes. Therefore, clinical endpoints that reflect certain aspects of improved glucose control have the potential to demonstrate meaningful benefit.